Evolution of coadaptation in a diploid population (Theory of Bio-Mathematics and It's Applications)

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Evolution of coadaptation in a diploid population

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Two models of epistatic selection without dominance are studied for their effects on fixation probabilities. Previously, on studying the evolution of coadaptation in a diploid population, we have found that two related but different models of epistasis produce distinct evolutionary predictions when the effect of linkage disequilibrium cannot be ignored. We here report simulation results that illustrate this discrepancy, and briefly discuss its implication for studies on epistatic selection in a diploid population.

Keywords: *cis-trans* effect, coadaptation, diploidy, epistasis, fixation probability, population genetics.

Precise understanding of the genetic basis of the evolution in multilocus systems is still very limited. A variety of mathematical models has been developed for studying multilocus evolutionary dynamics. In one extreme, it is assumed that the loci (or sites) are very tightly linked such that the genealogical history of the system may be described based on the standard (structured) coalescent framework with recombination (*e.g.* Barton & Navarro 2002). On the other extreme, in the classical prospective (forward-viewing) framework, it is rather customary to assume that the loci are only loosely linked such that the effects of linkage disequilibrium are negligible (*e.g.* Barton & Turelli 2004). Furthermore, even when one is interested in consequences of epistatic interactions, a simplified assumption of independence (or additivity) of alleles within each locus is often made so that a panmictic population of N diploids is equivalent to a corresponding haploid population of size $2N$ (*e.g.* Barton & Turelli 2004).

Previously, we have investigated two distinct models of epistatic selection without dominance, and found that they should produce, in certain conditions, different predictions regarding the fixation probability of a coadapted haplotype in a diploid population (Takahasi & Tajima 2005). Here, alleles at distinct loci are said to be coadapted if they together improve the ability of organisms to survive and reproduce (as exemplified in Table 1 for a haploid system with two diallelic loci). Whereas the prevalence of coadaptation in biological systems may be understood from, say, numerous observations of hybrid breakdown (*i.e.* disruption of coadapted allelic combinations through hybridization) in the wild (Templeton 1986; Hufford & Mazer 2003), the question regarding the mechanism of its evolution is still unresolved. (Interested readers should consult Takahasi & Tajima 2005 for backgrounds.)

On studying the simplest case without dominance, we first considered that the evolution in a diploid population could be described by a haploid model with constant (frequency-independent) haplotype fitnesses as depicted in Table 1. Assuming random mating and weak selection, it is easily verified that the assumption of haploid selection corresponds to the diploid case with epistasis in *cis*, where fitness increase is achieved only when two mutant alleles are combined in the coupling phase (Table 2a). This type of epistasis may arise in diploids when the interacting loci are relatively closely located on a chromosome (*e.g. cis*-regulatory elements; Kleinjan & van Heyningen 2005). However, when the two loci are not so closely linked along a chromosome, epistasis in *trans* may be better suited for describing genetic interactions in a diploid genome (Table 2b). In this case, fitness increase is achieved even when mutations at the two loci are combined in the repulsion phase. In the following, we illustrate the distinct characteristics of these two models of epistasis by focusing our attention to a specific situation where the two mutant alleles A_1 and B_1 are simultaneously introduced into a diploid population (*i.e.* if the time length T between the two consecutive mutational events is zero).

Given the fitnesses of two-locus genotypes as depicted in Table 2, the frequency dynamics of haplotypes in a panmictic population can be obtained based on the standard forward dynamics model with selection and recombination (*e.g.* equation 2.94 in Ewens 2004). The two models of epistasis should produce identical frequency dynamics as long as the two loci are in linkage equilibrium. However, distinct outcomes are expected when the linkage is tight and non-negligible amount of linkage disequilibrium should be established. Indeed, we have found that fixation probabilities are somewhat higher when *cis*-acting mutations are assumed.

Table 1. An example of two-locus coadaptation in a haploid organism ($s > 0$).

Haplotype	Fitness
A_1B_1	$1 + s$
A_1B_0, A_0B_1, or A_0B_0	1

– Alleles A_1 and B_1 interact synergistically to form a coadapted haplotype A_1B_1.

This incongruence may be best illustrated by considering the limiting case of no recombination (complete linkage). Without recombination, the fixation of the coadapted haplotype A_1B_1 is possible only when the two new mutations A_1 and B_1 (that are introduced simultaneously, with time interval $T = 0$) arise on the same chromosome. If this rare event should occur [with a probability of $1 / (2N)$], then the subsequent evolution leading to absorption (*i.e.* fixation or loss) is largely governed by the initial selective advantage of the coadapted haplotype when it is rare within the population, which is s for epistasis in *cis*, and $s / 2$ for epistasis in *trans* (Table 2). Further recalling that the fixation probability of a new mutation is approximately twice its (initial) selective advantage (*e.g.* see chapter 5 in Gale 1990), the ultimate probability for the fixation of the coadapted haplotype A_1B_1 in the absence of recombination becomes

$$2s / (2N) \tag{1}$$

for epistasis in *cis*, whereas it is only

$$s / (2N) \tag{2}$$

for epistasis in *trans*, which is just one-half of the corresponding probability for *cis*-acting mutations.

For models with recombination, we study the fixation probability using stochastic simulations that follow the forward dynamics of haplotype frequency changes in a panmictic population of N diploids. Stochastic dynamics were simulated by the improved version of the pseudosampling method (Kimura & Takahata 1983). Specifically, it is assumed that $N = 10{,}000$ and $s = .01$, with the recombination rate c ranging from .1 to the lower limit of 10^{-14}. As illustrated in Figure 1, the overall probability is consistently higher with *cis*-acting mutations. This is presumably because with epistasis in *cis*, selection promotes the combination of A_1 and B_1 alleles in the coupling phase, thereby facilitating the fixation of the haplotype A_1B_1. On the other hand, with epistasis in *trans*, selection favors these mutations also when they are in the repulsion phase, which may further hamper the evolutionary increase of the coadapted haplotype.

Table 2. Relative fitnesses of two-locus genotypes with *cis*- or *trans*-acting mutations.

Maternal gamete	Paternal gamete			
	A_1B_1	A_1B_0	A_0B_1	A_0B_0
a, Epistasis with *cis*-acting mutations				
A_1B_1	$1 + 2s$	$1 + s$	$1 + s$	$1 + s$
A_1B_0	$1 + s$	1	1	1
A_0B_1	$1 + s$	1	1	1
A_0B_0	$1 + s$	1	1	1
b, Epistasis with *trans*-acting mutations				
A_1B_1	$1 + 2s$	$1 + s$	$1 + s$	$1 + s / 2$
A_1B_0	$1 + s$	1	$1 + s / 2$	1
A_0B_1	$1 + s$	$1 + s / 2$	1	1
A_0B_0	$1 + s / 2$	1	1	1

Moreover, with *trans*-acting mutations, the convergence of the fixation probability to the limiting value of $s / (2N)$ [as $\log(c) \to -\infty$] shows rather complex behavior; it once reaches an approximate plateau near $2s / (2N)$ for recombination rates in the range $-9 < \log(c) < -5$, and then suddenly drops off to the expected value of $s / (2N)$ as the recombination rate approaches 10^{-10} or smaller.

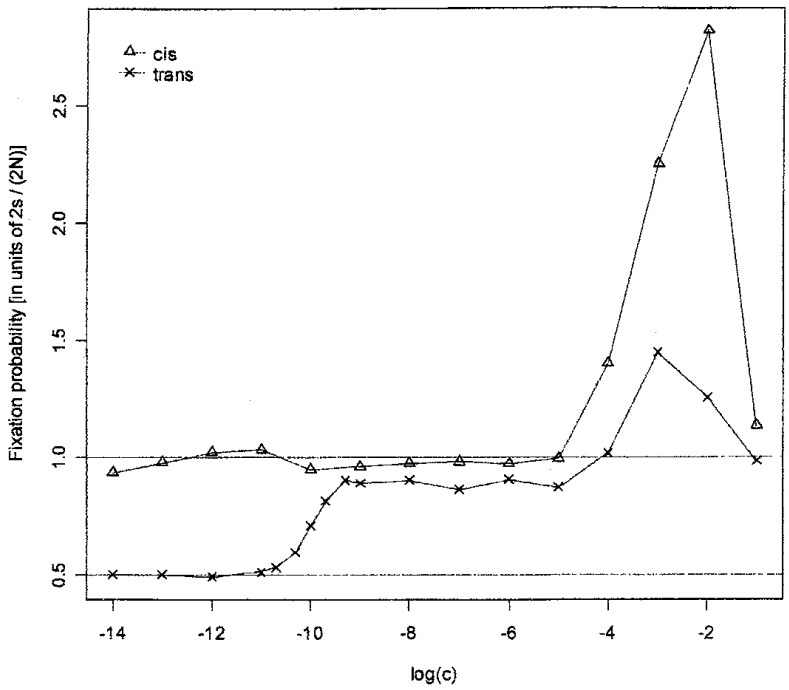

Figure 1. Fixation probabilities for models with *cis*- or *trans*-acting mutations. Probabilities for the fixation of the adaptive combination A_1B_1 are plotted as a function of the recombination rate between the two loci. The abscissa designates the logarithm of the recombination rate c, and the ordinate gives the fixation probability, scaled in units of $2s$ / ($2N$). In the simulations, we assume N = 10,000 and s = .01. The simulations are repeated until the fixation of the co-adapted haplotype is replicated for 1,000 times.

Many organisms are diploid, carrying chromosomes in pairs. Still, it has been customary in population genetics literature to posit the simplified assumption of haploidy, and properties of diploid populations have been inferred based on the haploid models. We do not doubt the utility of such simplified assumptions in studying genetics of populations, but at the same time, we have to be aware that there are situations where the assumption of haploidy should lead to predictions different from those obtained from models without such assumptions. As indicated, fixation probability under epistatic selection represents one of those examples.

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